Lyme disease: a review

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SUMMARY. In the last decade, Lyme borreliosis has emerged as a complex new infection whose distribution is worldwide. The multisystem disorder, which primarily affects the skin, joints, heart and nervous system at different stages, is caused by the tickborne spirochaete Borrelia burgdorferi. *After the first weeks of infection almost all patients have a positive antibody response to the spirochaete and serological determinations are currently the most practical laboratory aid in diagnosis. Treatment with appropriate antibiotics is usually curative.*

Introduction

RECOGNITION of Lyme disease is increasing in the United Kingdom. This article reviews the clinical features, diagnosis and treatment of this seasonal non-occupational bacterial zoonosis. It was first recognized in 1975, in the United States of America when a large cluster of children developed arthritis in Lyme, Connecticut.[1] It is found in numerous temperate zones around the world including Europe, Australia, China and the Soviet Union.

The disease is caused by the spirochaete *Borrelia burgdorferi* transmitted by the ixodes species of tick. In the UK, *Ixodes ricinus* is the main vector. Increasing numbers of cases of Lyme disease are being diagnosed in the UK particularly in the New Forest, Hampshire, and parts of Scotland.[2-4] The first British case was reported in a Hampshire child with arthritis in 1985.[5] The main hosts for the vector are large deer and small rodents, but domesticated animals, sheep, cattle and many bird species can also act as hosts.[6,7] The vector produces a multisystem disorder primarily affecting the skin, heart, central nervous system and joints.

Pathogenesis

The nymphal stage of the tick seems to be primarily responsible for the transmission of Lyme disease.[8] The peak period of activity for the nymphs is the spring and summer months which coincides with the usual period of presentation of the illness.[9,10] The spirochaete is injected by the bite into the skin or capillaries and after an incubation period of between three and 32 days it migrates outwards in the skin to produce the classical immune mediated skin lesion of erythema chronicum migrans.[11] It can then spread to regional lymph nodes or disseminate to organs such as the brain, heart and joints. The mechanism of the disease in the later stages is less certain and may either be due to persistent survival of the spirochaete in the affected organs or a chronic immune complex mediated inflammatory response.[12]

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Clinical features

Like other spirochaetal diseases such as leptospirosis, relapsing fever and syphilis, the progression of Lyme disease can be roughly divided into three stages (Figure 1),[13] although there is considerable overlap between the stages.

Stage 1 — skin conditions

The initial manifestation of Lyme disease is its hallmark — a rapidly expanding painless annular rash called erythema chronicum migrans. About one third of patients remember a tick bite which often leaves a small red macule or papule. Approximately one week after the bite this lesion expands to form a painless, hot, annular lesion. In 50% of patients there are multiple secondary lesions. The commonest sites affected are the thighs, axillae and groin.[14]

It must be emphasized that although a high percentage of patients have a history of an initial rash, some patients may present with a later stage of the disease without recalling skin manifestations. Two other, less frequent, but more chronic skin conditions have been described as late complications of Lyme disease. Acrodermatitis chronica atrophicans, a violaceous infiltration of the skin producing plaques or nodules, can present six months to eight years after the original infection while lymphadenosis benigna cutis, a lymphocytic infiltration of the skin presents as nodules in the skin of the ears, head or neck. Other possible dermatological associations are morphoea, a localized form of scleroderma,[15] and eosinophilic fasciitis.[16]

Stage 2 — cardiac and neurological abnormalities

In the second stage of Lyme disease, cardiac and neurological abnormalities can occur, the former in 8% of cases and the latter in 15% of cases.[17] Cardiac involvement which is thought to be less common in Europe than in the USA, occurs on average 21 days after the erythema chronicum migrans rash (Muhlemann MF, *et al.* Lyme borreliosis update Europe, Baden, Austria 1987; abstract no. 37). Patients, often young males, experience myocarditis with conduction system abnormalities. Patients usually present with syncope, palpitations and dyspnoea. The commonest electrocardiographic findings described are atrioventricular

Stage 1. Days to weeks after tick bite

Erythema chronicum migrans at site of tick bite

Constitutional features — fever, headaches, myalgia, stiff neck, arthalgia and lymphadenopathy

Stage 2. Weeks to months after rash if untreated

Neurological: meningitis, radicular neuritis and cranial neuritis, peripheral neuropathy

Cardiac: myocarditis, and/or conduction system abnormalities

Stage 3. Weeks to years after rash if untreated

Arthritis — mono- or oligo-articular; intermittent or chronic

Figure 1. *The clinical progression of Lyme disease.*

blocks and T wave abnormalities.[17] Hospital admission is recommended for patients with a PR interval of greater than 0.3 millimetres since this may herald complete heart block.[18]

Neurological presentation is classically a triad of meningitis, cranial neuritis and radicular neuritis.[19] Lymphocytic meningitis can occur about a month after the onset of the rash. There may be mild symptoms of encephalitis and if palsy occurs it is usually of the seventh nerve. It has been reported that oedema and erythema of the face are characteristic early signs of facial nerve involvement (Maskby DP. UK Lyme Disease Discussion Group, PHLS, December 1988). Radicular neuritis presents as a burning pain affecting a dermatome with or without weakness and loss of deep tendon reflexes. A large number of less common neurological manifestations have been described, reflecting a diverse and often atypical presentation.[10]

Stage 3 — joint abnormalities

Arthritis occurs in the third stage of Lyme disease. It has been reported in up to 60% of patients with the disease in the USA although in Europe the incidence has been reported to be much lower at 2%.[20] Symptoms usually occur between a few months and two years after the initial rash although there is considerable temporal overlap with the second stage. Typically there is a mono- or oligo-arthropathy of a large joint especially the knees (in 96% of cases), shoulders, ankles, elbows and the temporomandibular joints. Early in the illness the typical pattern is one of migratory musculoskeletal pain in joints, tendons, bursae, muscle or bone often with little joint swelling. Later, a few months after onset, patients experience characteristic intermittent arthritis. The attacks, which may last for a few weeks or months, typically recur over several years. About 10% of patients develop a chronic synovitis with joint erosion and permanent joint disability.[21] In children the disease mimics juvenile rheumatoid arthritis.

Other clinical manifestations

There are many other manifestations of Lyme disease. The skin lesions are often accompanied by non-specific symptoms such as headache, fever, malaise, myalgia, arthalgia and lymphadenophathy, while fatigue, headache, myalgia, arthalgia and lymphadenopathy often accompany neurological or joint disease. Ophthalmic problems,[22] hepatosplenomegaly and congenital infection[23] are much rarer associations.

Differential diagnosis

The broad spectrum of clinical manifestations in Lyme disase mimics a large number of diseases that need to be considered in the differential diagnosis.

The early systemic upset may be similar to many viral illnesses, including infectious mononucleosis, anicteric hepatitis and enteroviral (particularly coxsackie B) infection. The characteristic skin lesion may be mistaken for streptococcal cellulitis and the joint symptoms may be confused with juvenile rheumatoid arthritis, systemic lupus erythematosus or other collagen vascular disease. Cardiac problems may be misdiagnosed as rheumatic fever or viral myocarditis. Finally, the major neurological manifestation of aseptic meningitis may be confused with leptospiral, enteroviral or early tuberculous meningitis. Other neurological diseases that mimic Lyme disease include sarcoidosis, disseminated sclerosis and Mollaret's recurrent meningitis.

Diagnosis

The diagnosis of early Lyme disease is made on clinical grounds and often requires a high level of suspicion on the part of the doctor. A history of residence in or travel to an endemic area, a tick bite and an erythema chronicum migrans type rash occurring in the spring or summer should alert the doctor to the diagnosis. Treatment with an appropriate antibiotic should be initiated, although blood should be taken to try to confirm the diagnosis serologically — a 5–10 ml clotted sample is sufficient. However, serology is often ureliable at this early stage. Detection of specific antibody is currently the standard means of laboratory diagnosis. Specific immunoglobulin (Ig)M antibody usually reaches a peak between the third and sixth week after onset but specific IgG rises more slowly and generally peaks months or years later, usually when joint problems are present.[24] It is clear that serological testing at the time of skin presentation may show a negative or low titre, but a significant rise on later testing. Antibiotic therapy does not appear to affect the antibody response. The various diagnostic techniques (immunofluorescence, enzyme-linked immunosorbent assay, haemagglutination and immunoblotting) all have their pitfalls. Lack of specificity results from cross reaction with other treponemal disease such as syphilis, and collagen disorders and cross reaction may also result in low sensitivity. Immunoblotting and antigen detection techniques may offer better results than immunofluorescence or enzyme-linked immunosorbent assay.[25] Other non-specific abnormalities associated particularly with the early illness are a fast erythrocyte sedimentation rate, elevated serum IgM and mildly elevated glutamyl transferase and lactate dehydrogenase levels. Tests for rheumatoid factor and antinuclear factor are usually negative. Before accepting positive borrelia serology, *Treponema pallidum* haemagglutination from the venereal disease research laboratory should be negative.

Prevention

Lyme disease has been recognized in most part of the UK where ticks are present. Foresters, farmers, campers, orienteers and nature enthusiasts are among groups who may be considered at risk of infection. The risk following an individual tick bite is low but variable with maximum transmission being dependent on the nature of the spirochaete host (Smith HV, *et al.* UK Lyme Disease Discussion Group, PHLS, December 1988). In the New Forest public information in the form of leaflets is provided to ensure that rapid, practical and effective measures are taken by the individual following a tick bite. As it takes at least 72 hours for the nymphal tick to infect humans, daily inspection of the skin and removal of ticks could reduce the infection rate in endemic areas.[26]

Treatment

Early treatment with antibiotics stops the course of the disease and reduces the incidence of complications. Adults with erythema chronicum migrans should be treated with oral tetracycline 250 mg four times a day for at least 10 days and if symptoms persist for a further 10 days. Second line treatment is with oral penicillin V 500 mg four times a day or erythromycin 250 mg four times a day, in patients with penicillin allergy, for 10–20 days. In children where tetracyclines are contraindicated penicillin V 50 mg per kg a day is given in divided doses for the same duration and in penicillin allergy erythromycin 30 mg per kg a day in divided doses is given.[27,28] In pregnancy penicillin V 500 mg four times a day for 10–20 days is the first line therapy. The more chronic skin conditions, acrodermatitis chronica atrophicans and lymphadenosis benigna cutis, are less rapidly resolved by antibiotics.[29]

For neurological diseases a third generation cephalosporin, such as ceftriaxone[30] or cefotaxime,[31] seems to be superior to high dose intravenous benzylpenicillin, although the latter, which is often preferred by doctors, is also effective.[32] More recently oral tetracycline has also been used successfully.[33] Ceftriaxone has been found to be particularly effective in advanced Lyme

disease unresponsive to high dose benzylpenicillin.[34] Carditis associated with Lyme disease is normally self limiting and is not usually affected by antibiotic therapy; aspirin is normally given.[35]

Arthritis has been successfully treated with high dose intravenous benzylpenicillin for 10 days.[36] Aspirin or other non-steroidal anti-inflammatory agents are usually added to the regimen.

Conclusions

Although this eminently treatable condition is becoming increasingly recognized the diagnosis is often missed by general practitioners. Prevention and early treatment should be the hallmark of effective management. Increasing the awareness of the public and general practitioners would be a step in the right direction to achieving this goal.

References

1. Steere AC, Malawista SE, Snydman DR, *et al.* Lyme arthritis: an epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. *Arthritis Rheum* 1977; **20:** 7.
2. Muhlemann MF, Wright DJM. Emerging pattern of Lyme disease in the United Kingdom and Irish Republic. *Lancet* 1987; **1:** 260-262.
3. Bateman DE, Lauton NF, White JE, *et al.* The neurological complications of *Borrelia burgdorferi* in the New Forest of Hampshire. *J Neurol Neurosurg Psychiatry* 1988; **51:** 699-703.
4. Nathwani D, Hamlet N, Irwin G, Walker E. A survey of 32 Scottish cases of Lyme disease. *Communicable Diseases (Scotland) Unit Weekly Report* 1989; **2:** 8-12.
5. Williams D, Rolles CJ, White JE. Lyme disease in a Hampshire child — medical curiosity or beginning of an epidemic. *Br Med J* 1986; **292:** 1560-1561.
6. Burgdorfer W, Kierons JE. Ticks and Lyme disease in the United States. *Ann Intern Med* 1983; **99:** 121.
7. Donnelly J. The ecology of *Ixodes ricinus. PHLS Microbiology Digest* 1987; **4:** 52-53.
8. Steere AC, Malawista SE. Cases of Lyme disease in the United States: locations correlated with distribution of *Ixodes daminii. Ann Intern Med* 1979; **91:** 730.
9. Anderson JF, Maynarell LA. Vertebrate host relationships and distribution of ixodid ticks in south-central Connecticut, USA. *J Med Entomol* 1980; **17:** 891.
10. O'Neill PM, Wright DJM. Lyme disease. *Br J Hosp Med* 1988; **40:** 284-289.
11. Steere AC, Hardin JA, Malawista SE. Erythema chronicum migrans and Lyme arthritis: cryoimmunoglobulins and clinical activity of skin and joints. *Science* 1977; **196:** 1121-1122.
12. Steere AC, Malawista SE. Lyme disease. In: Mandal GL, Douglas RG, Bennett JE (eds). *Principles and practice of infectious diseases.* 2nd edition. Edinburgh: Churchill Livingstone, 1985: 1343-1349.
13. Petrie WA, Farr BM. Lyme disease. *Current Opinions in Infectious Diseases* 1988; **1:** 188-195.
14. Steere AC, Bartenhagen SE, Craft JE, *et al.* The early clinic manifestations of Lyme disease. *Ann Intern Med* 1980; **93:** 8.
15. Weber K, Preac-Mursic V, Reimers CD. Spirochetes isolated from two patients with morphoea. *Infection* 1988; **16:** 25-26.
16. Stanek G, Konrad K, Jung M, Ehringer H. Schulman syndrome, a sclerodermia subtype caused by *Borrelia burgdorferi. Lancet* 1987; **31:** 1490.
17. Steere AC, Batsford WP, Weinberg M, *et al.* Lyme carditis: cardiac abnormalities of Lyme disease. *Ann Intern Med* 1980; **93:** 8-16.
18. Olson LJ, Okafor EC, Clements IP. Cardiac involvement in Lyme disease: manifestations and management. *Mayo Clin Proc* 1986; **61:** 745-749.
19. Pacher AR, Steere AC. The triad of neurological manifestations of Lyme disease: meningitis, cranial neuritis and radiculoneuritis. *Neurology* 1985; **35:** 47-53.
20. Stanek G, Wewalka G, Groh V, *et al.* Differences between Lyme disease and European arthropod-borne borrelia infections. *Lancet* 1985; **1:** 401.
21. Steere AC, Schoen RT, Taylor E. The clinical evaluation of Lyme arthritis. *Ann Intern Med* 1987; **107:** 725-731.
22. Steere AC, Duroy PH, Kaufmann DJH, *et al.* Unilateral blindness caused by infection with the Lyme disease spirochete, *Borrelia burgdorferi. Ann Intern Med* 1985; **103:** 382-384.
23. Schlesinger PA, Duray PH, Burke BA, *et al.* Maternal foetal transmission of the Lyme disease spirochete *Borrelia burgdorferi. Ann Intern Med* 1985; **103:** 67-68.
24. Craft JE, Grodzick RL, Steere AC. Antibody response in Lyme disease: evaluation of diagnostic tests. *J Infect Dis* 1984; **149:** 789-795.
25. Guther SJ, Wright DJM. Serodiagnosis of Lyme disease. *Serodiagnosis and Immunotherapy in Infectious Disease* 1988; **2:** 4-6.
26. Hamlet N, Nathwani D. A report on the Scottish workshop on Lyme disease. *Communicable Diseases (Scotland) Unit Weekly Report* 1989; **22:** 7-8.
27. Steere AC, Malawista SE, Newman JH, *et al.* Antibiotic therapy in Lyme disease. *Ann Intern Med* 1980; **93:** 1.
28. Steere AC, Hutchinson GJ, Rahn DW, *et al.* Treatment of the early manifestations of Lyme disease. *Ann Intern Med* 1983; **99:** 22.
29. Asbrink E, Hovmark A. Cutaneous manifestations in ixodes-borne borrelia spirochaetosis. *Int J Dermatol* 1987; **26:** 215-233.
30. Dattwyler RJ, Halperin JJ, Volkmann DJ, Luft BJ. The treatment of late Lyme borreliosis — randomised comparison of ceftriaxone and penicillin. *Lancet* 1988; **1:** 1191-1197.
31. Pal GSI, Baker BJ, Wright DJM. Penicillin resistant borrelia encephalitis responding to cefotaxime. *Lancet* 1988; **1:** 50-51.
32. Steere AC, Pachner AR, Malawista SE. Successful treatment of neurological abnormalities of Lyme disease with high dose intravenous penicillin. *Ann Intern Med* 1983; **99:** 767.
33. Ackley A, Lupovici M. Lyme disease meningitis treated with tetracycline. *Ann Intern Med* 1986; **105:** 630-633.
34. Hedberg CW, Osterholm MT, MacDonald KZ, White KE. Ceftriaxone as effective therapy in refractory Lyme disease. *J Infect Dis* 1987; **155:** 1322-1325.
35. Steere AC, Green J, Hutchison GJ, *et al.* Treatment of Lyme disease. *Zentralbl Bakteriol Mikrobiol Hyg* [*A*] 1986; **263:** 352-356.
36. Steere AC, Green J, Schoen RT, *et al.* Successful parenteral penicillin therapy of established Lyme arthritis. *N Engl J Med* 1985; **312:** 869-874.

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